REMARKS

Previously, claims 23-58 were pending. In the instant amendment, claims 23-25, 28-30 and 58 have been amended. After entry of the amendments to the claims, claims 23-58 will be pending and under consideration.

I. AMENDMENTS TO THE SPECIFICATION

The priority claim on the first page of the specification, as amended in the Preliminary Amendment mailed September 8, 2003, has been amended in the instant amendment to reflect that the parent application, U.S. Application No. 09/735,707 has issued as U.S. Patent No. 6,680,203.

No new matter is added with this amendment. Entry thereof is respectfully requested.

II. AMENDMENTS TO THE CLAIMS

Claims 23-25, 28-30 and 58 have each been amended to correct typographical errors. In particular, claim 23 has been amended to recite a second peak "profile" in step (a) according to its antecedent. Claims 23-25 have each been amended with the addition of the word "at" to step (b). Claims 28-30 have been amended with respect to the identification of the steps recited. Claim 58 has been amended to depend from claim 57.

Claims 23-25 have also been amended to recite, in pertinent portion, "thereby at least one molecule that differs in abundance between a first cell population and a second cell population is identified."

The amendments to the claims are fully supported by the specification and claims as originally filed. No new matter has been added in the instant amendments. Entry thereof is respectfully requested.

Since the instant amendments to the claims do not add new multiple or independent claims, nor change the total number of claims, no claim amendment fee is believed to be due in connection with the amendments to the claims.

III. PRIORITY

The Patent Office requests that the priority claim be updated to reflect that the parent application, U.S. Application No. 09/735,707 has issued as U.S. Patent No. 6,680,203. The objection is obviated in view of the instant amendment to the specification.

The Patent Office states that the U.S. Application No. 09/735,707 is improperly named CIP of the provisional application. A copy of a corrected filing receipt that is

concurrently being sent to the Office of Initial Patent Examination's Filing Receipt Corrections is enclosed.

IV. DOUBLE PATENTING

Claims 23-58 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable allegedly over claims 1-32 of U.S. Patent No. 6,680,203. Applicants respectfully request that the rejection be held in abeyance until the form of the instant claims are otherwise found to be allowable at which point Applicants will consider filing a Terminal Disclaimer over claims 1-32 of U.S. Patent No. 6,680,203.

V. RESPONSE TO CLAIM OBJECTIONS

The Patent Office objects to claims 23-25 on the basis of informalities consisting of typographical errors in step (b) of claim 23 (missing the word "at"), typographical errors in the "thereby clause" in claims 23-25, and improper dependence to claim 5747 in claim 58. The objections to claims 23-25 are overcome in view of the amendments to the claims.

Included in the objection to claims 23-25, the Patent Office contends that the "thereby clause" is a repetition of step (c). Claims 23-25 have been amended to clarify that this clause is not a step in the method.

Accordingly, Applicants respectfully request that the objection to claims 23-25 be withdrawn.

VI. CLAIM REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 23 and 24 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness allegedly with regard to the phrases "wherein the first peak profile and the second peak profile are obtained independently" in claim 23 and "are not obtained concurrently" in claim 24. Claims 55 and 56 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness allegedly with regard to the phrases "wherein the first peak profile is a historical control" in claim 55 and "wherein the first peak profile is a concurrent control" in claim 56.

A. Claims 23 and 24

Claims 23 and 24 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness allegedly with regard to the phrases "wherein the first peak profile and the

second peak profile are obtained independently" in claim 23 and "are not obtained concurrently" in claim 24. Applicants respectfully traverse.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories Inc. v. Shandon Inc.*, 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993) *cert. denied* 510 U.S. 1100 (1994). "The purpose of the claims is not to explain the technology or how it works, but to state the legal boundaries of the patent grant. A claim is not 'indefinite' simply because it is hard to understand when viewed without benefit of the specification." S3 Inc. v. nVIDIA Corp., 59 U.S.P.Q.2d 1745, 1748 (Fed. Cir. 2001).

The Patent Office contends that the terms "independently" and "concurrently" are not clear since it is not apparent how the first and second peak profiles can be obtained "dependently" or "concurrently." Applicants respectfully disagree, since there are any number of ways to obtain different peak profiles dependently or concurrently. For example, two cell extracts can be combined where the product of one cell extract only is treated with a known chemical entity to change the product's mass to charge ratio, and then, within the mass spectroscopy spectrum of the combined cell extracts, the peak profile of the product from the untreated cell extract can be compared with the peak profile of the product from the treated cell extract within that spectrum. Applicants respectfully submit that one skilled in the art would understand the bounds of claim 23 with regard to the phrase "wherein the first peak profile and the second peak profile are obtained independently" and the bounds of claim 24 with regard to the phrase "are not obtained concurrently" when read in light of the specification.

Accordingly, Applicants respectfully request that the rejection of claims 23 and 24 under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Claims 55 and 56

Claims 55 and 56 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness allegedly with regard to the phrases "wherein the first peak profile is a historical control" in claim 55 and "wherein the first peak profile is a concurrent control" in claim 56. Applicants respectfully traverse.

A "control" is a "standard of comparison for checking or verifying the results of an experiment." *See* page 303, The American Heritage College Dictionary, Third Edition (Houghton Mifflin Co. 1997) (definition 4a). "Concurrent" is defined as "operating or acting in conjunction with another." *See* page 289, The American Heritage College Dictionary,

Third Edition (Houghton Mifflin Co. 1997) (definition 2). The specification explains that a test sample can be compared to a reference sample and that the "reference sample can be predetermined, i.e., is a historical sample." *See* page 44, lines 27-28, Specification.

Applicants respectfully submit that one skilled in the art would understand the bounds of claims 55 and 56 when read in light of the specification. *See Miles Laboratories Inc. v. Shandon Inc.*, 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993) *cert. denied* 510 U.S. 1100 (1994). Specifically, with regard to claim 55, "wherein the first peak profile is a historical control" means that the first peak profile is predetermined. This stands in contrast to the first peak profile in claim 56 that is a "concurrent control" obtained in conjunction with the second peak profile and which serves as a standard of comparison for the second peak profile.

Accordingly, Applicants respectfully request that the rejection of claims 55 and 56 under 35 U.S.C. § 112, second paragraph, be withdrawn.

VII. CLAIM REJECTION UNDER 35 U.S.C. § 103(a)

Claim 23 stands rejected under 35 U.S.C. § 103(a) as being obvious over Crooke *et al.* (U.S. Patent No. 6,329,146) in view of Southern *et al.* (U.S. Patent No. 5,70,367). Applicants respectfully traverse.

A. The Legal Standard

To establish a *prima facie* case of obviousness in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill to select the references and combine them in the way that would produce the claimed invention. *See Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001). Moreover, the prior art must reveal that in so making or carrying out the claimed invention, those of ordinary skill would have a reasonable expectation of success. *See e.g., In re Vaeck*, 20 U.S.P.Q.2d 1438,1442 (Fed. Cir. 1991).

"A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). In particular, the Examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *See In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988).

Applicants respectfully submit that the Patent Office has not established a *prima facie* case of obviousness, and in raising the obviousness rejection, is employing, perhaps unconsciously, a hindsight reconstruction. As stated above, hindsight reconstruction does not meet the legal standard for obviousness. Neither of the references cited by the Patent Office, alone or in combination, teaches or suggests the method of claim 23, let alone an expectation of success of carrying out the method.

B. Claim 23 is Not Obvious Over Crooke *et al.* and/or Southern *et al.*

Claim 23 recites a method comprising comparing Fourier Transform Mass Spectrometry (FTMS) peak profiles, *inter alia*, in which at least one molecule that differs in abundance between a first cell population and a second cell population is identified.

Applicants respectfully submit that the assay disclosed in Crooke *et al.* substantially differs from the method of instant claim 23. In particular, Crooke *et al.* teaches *in vitro* mass spectrometric screening methods entailing contacting a biomolecule or a population of a single type of biomolecule (such as RNA) that is labeled with a large molecular weight mass modifying tag with a ligand of interest and detecting the binding of the molecule to the ligand. The Patent Office acknowledges that Crooke *et al.* does not teach or suggest performing FTMS on whole cells. If anything, Crooke *et al.* teaches away from the use of FTMS for whole cell screening and analysis. In particular, column 7, lines 24-30 of Crooke *et al.*, states that:

> When screening multiple target nucleic acids, for example, mass redundancy is a concern, especially if two or more targets are of similar sequence composition or mass. This problem is alleviated by the present invention, by using special mass modifying, molecular weight tags on the different nucleic acid targets being studied. These mass modifying tags are typically large molecular weight, non-ionic polymers including but not limited to, polyethylene glycols, polyacrylamides and dextrans, that are available in many different sizes and weights, and which may be attached at one or more of many different possible sites on nucleic acids.

Thus, Crooke *et al.* states that molecules with similar molecular weights are unlikely to be resolved by mass spectrometry without the use of "special mass modifying molecular weight tags." In contrast, the method of instant claim 23 can be applied with a 2-3 ppm resolution (see specification at page 59, lines 21-26 and page 31, lines 16-21). Unlike the method of Crooke *et al.*, which can be performed using any type of mass spectrometry, the method of claim 23 requires the accuracy and resolution of FTMS. Accordingly, Crooke *et al.*, if

anything, teaches away from the method of claim 23, which encompass the analysis of complex whole cell peak profiles without requiring the use of molecular weight tags, many of which peaks correspond to molecules with very similar molecular weights.

Southern *et al.* does not remedy the deficiencies of Crooke *et al.* Southern *et al.* discloses assays for detecting the binding of labeled analytes to target substances. The labeled analytes are labeled in a manner that is "adapted for detection by mass spectroscopy," *i.e.*, the mass modifying molecular weight tags of Crooke *et al.*. The assays of Southern *et al.*, such as nucleic acid sequencing, are performed *in vitro*. Southern *et al.*, at column 11, lines 52-65 states:

> Many drugs are tissue-specific. Their action often depends on interaction with a cell-surface receptor. There are families of drugs based on core structures; for example, there are several comprising short peptides. It is useful to be able to trace candidate drugs to see which cells or tissues they may target. It would be useful to be able to trace many different candidates simultaneously. Using libraries of analytes tagged with coded mass-tags, it would be possible to trace interactions by examining cells or tissues in the mass spectrometer. If tags were attached by photolabile protecting groups, it would be possible to image whole animal or tissue sections using scanning laser cleavage, coupled with mass spectrometry.

The method suggested by Southern *et al.* is vastly different from the method of instant claim 23. The method of Southern *et al.* is for "tracing" tagged-drug/analyte interactions with cell-surface receptors. At best, Southern *et al.* suggests a method that entails contacting a tissue (or animal) with a drug/analyte labeled with a mass tag via a photolabile protecting group, then subjecting the tissue (or animal) to a scanning laser to cleave the tag, and determining the presence of the tag by mass spectrometry. Thus, Southern *et al.* suggests mass spectrometry for detection of exogenously introduced drugs/analytes that interact with cell receptors. Southern *et al.* does not teach or suggest the use of FTMS for analyzing whole cell contents to identify peaks that correspond to molecules that differ in abundance within the cells.

Southern *et al.* discloses that a molecular mass tag is required to identify the drug/analyte that target particular cells or tissues, and therefore, like Crooke *et al.*, teaches away from the method of instant claim 23 that encompasses the identification of peak profiles in cell populations without requiring the use of molecular weight tags. Additionally, the method of Southern *et al.* requires the experimenter search for the presence of a predetermined molecule that interacts with a cell, whereas the present method of claim 23 offers the advantage of *de novo* identification of molecules that are differentially present

among different cell populations. Thus, Southern *et al.*, whether alone or in combination with Crooke *et al.*, does not teach or suggest practicing the method of claim 23, let alone doing so with a reasonable expectation of success.

For these reasons, Applicants respectfully request that the rejection of claim 23 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Patent Office reconsider this application with a view towards allowance.

No fees, other than for the enclosed Petition for Extension of Time, are believed to be due. However, the Commissioner is hereby authorized to charge any necessary fee(s) under 37 C.F.R. § 1.17, any other required fee(s), or credit any overpayment to Jones Day Deposit Account No. 50-3013 (371855-999099).

Respectfully submitted,

Date: February 22, 2005 54,398

Roger C. Rich for
Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939